UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/547,669	09/02/2005	Daniele Calistri	2503-1170	1643

466 7590 03/10/2010

YOUNG & THOMPSON
209 Madison Street
Suite 500
Alexandria, VA 22314

EXAMINER	
STAPLES, MARK	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
03/10/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketingDept@young-thompson.com

Office Action Summary	Application No.	Applicant(s)	
	10/547,669	CALISTRI ET AL.	
	Examiner	Art Unit	
	MARK STAPLES	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9,10 and 12* is/are pending in the application.

4a) Of the above claim(s) *12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 9, and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/16/2010 has been entered.

2. Applicant's amendment of claim 1 in the paper filed on 02/16/2010 is acknowledged.

Claims 1, 9, and 10 consonant with original election of SEQ ID NOs: 9, 10, 13, 14, 15, and 15 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Declaration under 37 CFR 1.132 is insufficient

3. The Declaration under 37 CFR 1.132 filed 01/22/2009 is insufficient to overcome the rejections of pending and at issue claims 1, 9, and 10 based upon Shuber (2001), Kmiec et al. (W0 2001/73002), Albertsen et al. (US Patent No.: 6,114,124 issued 2001), and Buck et al. (1999) under 35 U.S.C. 103(a) as set forth in the last Office action

because: the differences in results of the instantly claimed primers and the “new” primers are not unexpected in view of the cited prior art, as follows.

Table 1: Results of FL-DNA analysis using different primers

It is acknowledged that results of claimed and “new” primers in Table are different. However, no evidence is presented that this difference is unexpected or that the results of the claimed primers are superior to the results of the “new” primers.

Table 2: Sensitivity and specificity of FL-DNA analysis with “claimed’ and "new” primers

It is acknowledged that several results of claimed and “new” primers in Table are different. It is also noted that specificity for instantly claimed and new primers is equivalent at the 15 ng cutoff, being 70% both for instantly claimed and new primers. The specificity of the instantly claimed primers is lower/inferior at the other cut-offs versus the “new" primers. In Table 2, the sensitivity of the instantly claimed primers is higher/superior for each cutoff listed. In particular, the sensitivity of the claimed priors is 50% or more higher/superior at the 20, 25, and 30 ng cut-offs. Overall the improvements in sensitivity of the claimed primers as seen in the actual numbers reported are offset at least to some degree by the inferior specificity of the claimed primers as versus the “new” primers. Thus taking the results of both sensitivity and specificity in total, Examiner finds that the range of the results of the claimed primers compared with the range of results of the prior art primers ("new" primers) are close enough, that one of ordinary skill in the art would have been able to optimize the methods the new primers and/or other factors in order to obtain improved and similar results.

Applicant conveys that the claimed primers with cutoffs of 10-15 or 20 ng yields more consistent results for both sensitivity and specificity than the new primers. Yet the data indicate that optimization of the "new" primers would have been expected to achieve these results, or similar results. Firstly, it is noted that the data support that trends of results towards higher or lower percentages are predictable, and hence in the cut-off range of 15-20 ng, one skilled in the art would have expected to achieve results of consistent sensitivity and specificity of the new primers similar to those of the claimed primers through titration of the cut-off in the range of 15-20 ng. In the range of 15-20 ng one would expect to achieve sensitivity of 50-10% and specificity of 70-100% for the "new" primers. In other words, one of skill in the art would have been able to titrate between 15 and 20 ng in order to achieve a high sensitivity with a high specificity for the new primers. Secondly, factors other than the primer sequences could be optimized to enhance the results of the new primers.

Furthermore the optimization of amplification through selection of primer sequences and other factors results was known in the prior art as taught by Shuber:

> "Each of the methods described above are based upon the principle that an intact nucleic acid, or a segment of an intact nucleic acid, in a sample is diagnostic. Thus, variations on the methods described above are contemplated. Such variations include the **placement of primers**, the number of primers used, the target sequence, the **method for identifying sequences, and others**. For example, in the method depicted in Figure 13, and described above, it is not necessary that the numbers of forward and reverse primers be equal. A forward primer may, for example, be used to amplify fragments between two reverse primers. **Other variations in primer pair placement** are within the skill in the art, as are details of the amplification reactions to be conducted. Finally, as represented in Figures 12 and 13, capture probes may be used in methods of the invention in order to isolate a chosen target sequence" (emphasis by Examiner, see the 1st paragraph on p. 17).

Likewise, Buck et al. taught that amplification methods, while tolerant of the sequences selected for primers to obtain amplification of a target sequence, gives variability in results depending on the primers used (entire article, especially the statistics of the average, median, and range in Table 2). Thus Buck et al. taught as well that variation in results is expected based upon the primer sequences selected.

Kmiec et al. also taught that variability from the selection of oligonucleotide primers was expected (see last paragraph on p. 34 continued to p. 35).

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers of the APC gene and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al (1999) expressly provides evidence of the equivalence of primers for achieving amplification of a target nucleic acid. Specifically, Buck invited primer

submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success. Buck et al., also teach the measured results vary with the selection of the primer sequences and along with Shuber and Kmiec et al. teach that the selection of primer sequences and other factors can be optimized to improve results.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Objections and Rejections that are Withdrawn

Claim Rejections Withdrawn - 35 USC § 112 Second Paragraph

4. The rejection of claims 1, 2, and 10 under 35 USC § 112 Second Paragraph is withdrawn as Applicant has amended claim 1 to overcome this rejection.

Rejections that are Maintained

Claim Rejections Maintained - 35 USC § 103

5. The rejection of claims 1, 9, and 10 under 35 U.S.C. 103(a) as being unpatentable over Shuber (2001, previously cited), Kmiec et al. (W0 2001/73002, previously cited), Albertsen et al. (US Patent No.: 6,114,124 issued 2001, previously cited), and Buck et al. (1999, previously cited) is maintained. Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that that Buck et al. had a different main objective than the instant methods and teaches the amplification of "high quality" DNA rather than DNA extracted from stool as claimed. However, Buck is relied upon for the teaching of the expectation of successful amplification with primers selected across the known region of a target nucleic acid sequence. Shuber, and not Buck et al., is primarily relied upon for the amplification of the DNA from stool. Furthermore, Applicant argues but does not present evidence that variation of primer sequences would not be successful in the present methods. It is noted that Applicant improperly submits (see the section for Information Disclosure Statement below) the post filing reference of Loktionov et al. but that this reference, while providing evidence that the quality DNA influences results ,

does not provide evidence that the selection of primer sequences influences the results. Furthermore, Applicant does not specifically cite part by page no. and paragraph, for example, of the reference supporting the contention that amplification of DNA from stool is more sensitive to the selection of primer sequences than other types of amplification, including those amplification methods taught by Buck et al. and especially in combination with the teachings of Shuber.

Response to Applicant's arguments regarding the data in declaration are found above. Some of the data in the declaration are also found in the article by Calistri et al. (2004). Neither does this article, however, provide data of unexpected results of the claimed primers over the cited prior art. The article presents data showing superior results with a fluoresence method versus a non fluorescence method. However, the rejection in view of prior art fluorescence methods, and is not made in view of non fluorescence methods.

At this time Examiner does not find that there is sufficient evidence in support of the claimed methods being unobvious or providing unexpected results. The results are within the expected variation for selection of primer sequences as taught in the prior art and could have been achieved through routine optimization by one of ordinary skill in the art at the time of the claimed invention.

Therefore the rejection is maintained.

New Rejection

Improper Information Disclosure

6. The information disclosure statement filed on 02/16/2010 within Applicant Arguments/Remarks Made in Amendment fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the content requirements as discussed in MPEP § 609.04(a) are not complied with and because copies of non-patent literature have not been provided. The references of Cancer Research 58:3957-64, 1998; Analytical Biochemistry 18:197-208, 1989; and PCR Methods and Applications 4:234-238, 1995 have not been provided and are not considered. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Applicant is advised to submit a proper information disclosure statement (IDS) which lists and provides the missing references. Applicant need not re-submit the references of Lokionov et al. and Calistran et al. but should provide a proper Information Disclosure listing them in response to this action. Should Applicant wish to provide support from the references for points or arguments made, Applicant should specifically cite where such support may be found within the reference, preferably by page and paragraph, figures, and/or tables.

Conclusion

7. No claim is free of the prior art.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark Staples/
Primary Examiner, Art Unit 1637
March 2, 2010